TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

Attorney's Docket Number	U.S. Application No.
02481.1699	09/646986

International Application. No.	International Filing Date	Priority Date Claimed
PCT/EP99/01729	March 17, 1999	March 27, 1998

Title of Invention: MINIATURIZED MICROTITER PLATE FOR HIGH THROUGHPUT SCREENING

Applicant For DO/EO/US: Henning VOLLERT

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. [X] This is a FIRST submission of items concerning a filing under 35 U.S.C. 371.
2. [ ] This is a SECOND or SUBSEQUENT submission of items concerning a filing under 35 U.S.C. 371.
3. [ ] This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. [ ] A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. [X] A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. [ ] is transmitted herewith (required only if not transmitted by the International Bureau).
   b. [X] has been transmitted by the International Bureau.
   c. [ ] is not required, as the application was filed in the United States Receiving Office (RO/US).
6. [X] A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. [X] Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3)).
   a. [ ] are transmitted herewith (required only if not transmitted by the International Bureau).
   b. [ ] have been transmitted by the International Bureau.
   c. [ ] have not been made; however, the time limit for making such amendments has NOT expired.
   d. [X] have not been made and will not be made.
8. [ ] A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. [X] An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. [ ] A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern other document(s) or information included:

11. [X] An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. [X] An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. [X] A FIRST preliminary amendment.
    [ ] A SECOND or SUBSEQUENT preliminary amendment.
14. [ ] A substitute specification.
15. [ ] A change of power of attorney and/or address letter.

16. [ ] Other items or information:
    a. [ ] Verified Small Entity Statement.
    b. [ ] Copy of Notification of Missing Requirements.

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U.S. APPLICATION NO.	INTERNATIONAL APPLICATION NO.	ATTORNEY DOCKET NUMBER
09/646986	PCT/EP99/01729	02481.1699

17. [X] The following fees are submitted:	CALCULATIONS
Basic National Fee (37 CFR 1.492(a)(1)-(5)):	
Search Report has been prepared by the EPO or JPO.....$840.00	
International preliminary examination fee paid to USPTO (37 CFR 1.482).....$670.00	
No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2)).....$690.00	
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO.....$970.00	
International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(1)-(4).....$ 96.00	
ENTER APPROPRIATE BASIC FEE AMOUNT =	**$840.00**
Surcharge of $130.00 for furnishing the oath or declaration later than **[ ] 20 [ ] 30** months from the earliest claimed priority date (37 CFR 1.492(e)).	$

Claims	Number Filed	Number Extra	Rate	
Total Claims	9 -20=		X $18.00	$
Independent Claims	1 - 3=		X $78.00	$
Multiple dependent claim(s) (if applicable)			+$260.00	$
TOTAL OF ABOVE CALCULATIONS =				**$840.00**
Reduction by 1/2 for filing by small entity, if applicable. Verified Small Entity statement must also be filed. (Note 37 CFR 1.9, 1.27, 1.28)				$
SUBTOTAL =				**$840.00**
Processing fee of $130.00 for furnishing the English translation later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492(f)).			+	$
TOTAL NATIONAL FEE =				**$840.00**
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31).		$40.00 per property	+	**$40.00**
TOTAL FEES ENCLOSED =				**$880.00**
Amount to be refunded				$
charged				$

a. [X] A check in the amount of **$ 880.00** to cover the above fees is enclosed.

b. [ ] Please charge my Deposit Account No. _____ in the amount of $_____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. [X] The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 06-0916. A duplicate copy of this sheet is enclosed.

The Commissioner is hereby authorized to charge any other fees due under 37 C.F.R. §1.16 or §1.17 during the pendency of this application to our Deposit Account No. 06-0916.

SEND ALL CORRESPONDENCE TO:
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ERNEST F CHAPMAN
Reg. No. 25,961

Submitted: September 26, 2000

PATENT
Attorney Docket No. 2481.1699

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	)	
	)	
Henning VOLLERT	)	
	)	
Serial No.: UNKNOWN, based upon PCT EP99/01729	)	Group Art Unit: Unknown
	)	
Filed: September 26, 2000	)	Examiner: Unknown
	)	
For: MINIATURIZED MICROTITER PLATE FOR HIGH THROUGHPUT SCREENING	)	

Assistant Commissioner for Patents
Washington, DC 20231

Sir:

PRELIMINARY AMENDMENT

Prior to the examination of the above application, please amend this application as follows:

IN THE SPECIFICATION:

Please amend the specification with reference to its numbered lines as follows:

Page 3, line 36, please change "c" to -- (c) --; and

line 37, please change "c1" to -- (c1) --.

IN THE CLAIMS:

Please cancel claims 1-4 and add new claims 5-13 as follows:

--5. A miniaturized microtiter plate comprising:

a plastic body;

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a glass base, the base of the microtiter plate having a thickness ranging from 0.07 to 0.2 mm;

a number of vessels for containing samples, wherein the number of vessels ranges from 1000 and 4000 vessels, the diameter of the vessels ranges from 1.0 to 1.8 mm, and the distance between the center of the outer vessels and an edge of the glass base ranges from 4 to 11 mm; and

a lid to prevent evaporation.

6. The miniaturized microtiter plate of claim 5, wherein the number of vessels ranges from 1400 to 2500, the diameter of the vessels ranges from 1.2 to 1.5 mm, and the thickness of the base ranges from 0.12 to 0.17 mm.

7. The minaturized microtiter plate of claim 5, wherein there are 1536 vessels.

8. The minaturized microtiter plate of claim 6, wherein there are 1536 vessels.

9. The miniaturized microtiter plate of claim 5, wherein the thickness of the base is 0.15 mm.

10. The miniaturized microtiter plate of claim 6, wherein the thickness of the base is 0.15 mm.

11. The miniaturized microtiter plate of claim 8, wherein the thickness of the base is 0.15 mm.

12. The miniaturized microtiter plate of claim 5, wherein the base is coated with a substance to suppress nonspecific binding.

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13. The miniaturized microtiter plate of claim 5, wherein the base is coated with a substance to encourage specific binding.

REMARKS

The specification has been amended to place it in proper U.S. format, and to correct grammatical and idiomatic errors. Claims 1-4 have been canceled and new claims 5-13 have been added to correct improper multiple dependency and provide claims in proper U.S. format.

If there is any fee due in connection with the filing of this Preliminary Amendment, please charge the fee to our Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.

Dated: September 26, 2000

By: Elizabeth M Burke
Elizabeth M. Burke
Reg. No. 38,758

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MINIATURIZED MICROTITER PLATE FOR HIGH THROUGHPUT SCREENING

The invention relates to a miniaturized microtiter plate for HT screening (high throughput screening).

In this screening it is desirable to minimize the consumption of assay components and of the substances from the screening libraries and to maximize the throughput of screening assays. This can be achieved by miniaturizing screening assays. However, it is necessary in this case to charge appropriate microtiter plates having an assay volume of about 0.5 to 10 µl, preferably 1 to 6 µl, particularly preferably 1 to 2 µl. The only ones available to date are a few prototypes which can be processed only by particular analyzers. However, there is a need for microtiter plates which permit analysis with very sensitive detectors (with confocal optics) and allow charging with "nanodispensers". A further desirable feature is prevention of evaporation.

Microtiter plates have been disclosed by Greiner, 64943 Hirschberg, (Micro-Assay Plate, 1536 wells). In this case, the effective volume of the sample carriers is relatively large (4-8 µl) and they do not permit "single molecule detection". Although the effective volume of the Corning Costar microtiter plates (Corning Costar Deutschland, 55924 Bodenheim) is between 1 and 2 µl, the frame of the microtiter plates is too thin so that conventional robotic systems are unable to transport the microtiter plates. "Single molecule detection" is impossible in this case, too. A Hellma brochure (1994) "Silica Glass Microassay Plates" discloses microassay plates with a base made of silica glass and 384 wells with a diameter of 3.5 mm. However, besides the large assay volume, these microassay plates have frames which are insufficiently broad and bases which are too thick (> 1 mm) to allow analysis using confocal optics. US 5,487,872 describes multiassay microtiter plates for UV spectroscopy having glass plates with a minimum thickness of 0.38 mm. These microtiter plates are also unsuitable for analysis using confocal optics. Microassay plates with lids to prevent evaporation are described in a Radleys brochure (1997) "Specialist Micro Titer Plates & Accessories".

The object of the invention is to provide a remedy for this.

This takes place according to the invention by a miniaturized microtiter plate which has a body made of plastic and a base made of glass and has 1000 to 4000 vessels (wells), preferably 1400 to 2500 vessels (wells), particularly preferably 1536 vessels (wells), the diameter of the vessels (wells) is approximately 1.0 to 1.8 mm, preferably 1.2 to 1.5 mm, the base of the microtiter plate has a thickness of 0.07 to 0.2 mm, preferably 0.12 to 0.17 mm, particularly preferably 0.15 mm, the distance between the center of the outer vessels (wells) and the edge of the glass base is 4 to 11 mm, preferably ≥ (greater than/equal to) 5.5 mm and the microtiter plate has a lid to prevent evaporation.

The miniaturized microtiter plate usually has a size of 10.0-15.0 x 7.0-10.0 cm, preferably 12.7 x 8.5 cm. However, sizes differing from this are also possible.

The shape of the vessels (wells) is variable. Thus, for example, vessels which are round, have corners or have rounded corners can be used. Round vessels are preferred. It is likewise possible for the number of vessels (wells) to differ from the abovementioned values. The angle between base and wall of the wells can vary between 20° and 90°.

It is important to use the correct material to produce microtiter plates. The body of the microtiter plate consists of plastic such as, for example, polystyrene, polypropylene, polycarbonate, Vectra®, Hostalen®, Topas®. The microtiter plates are usually produced by injection molding (or embossing). The plastic cools after the injection molding. Warping of the microtiter plate is possible during this (because of local differences in the rate of cooling). It is thus beneficial to use a material which produces only a very slight "curvature".

The lid of the microtiter plate is likewise made of plastic and sits form-fittingly on the microtiter plate. The thickness of the base (material: glass) of the microtiter plate (0.07 - 0.20 mm) and the diameter of the vessels (about 1.0 - 1.8 mm), and the distance between the center of the outer vessels (wells) and the edge of the glass base, which is 4 to 11 mm, allow analysis of the microtiter plate using confocal optics. The use of confocal optics has the following advantages:

1. The sensitivity is very high (compared with non-confocal optics) since even individual molecules can be detected in some circumstances (single molecule detection)

2. Because the sensitivity is high, the measurement time can be less and thus the overall rate of analysis of a microtiter plate can be increased (compared with many non-confocal optics) .

3. Since the focus of confocal optics is very small (usually distinctly less than 10 µm), detection of background signals is greatly reduced and thus the signal/noise ratio is better (compared with non-confocal optics).

The base, which consists of glass, of the microtiter plate can be coated with various chemical and biological substances, such as, for example, cellulose, cellulose derivatives, dextrans, polyethylene glycols, in order to suppress nonspecific binding. It ought likewise to be possible for the base to carry biological molecules which specifically bind other substances. The latter is important for use in drug screening, for example for sandwich assays.

Possible embodiments of the microtiter plate according to the invention are described in detail below with reference to Figures 1 to 3. The invention is, however, not restricted to these embodiments.

Fig. 1: Perspective depiction of the microtiter plate with lid lifted off

Fig. 2: Section along plane II-II from Fig. 1

Fig. 3: Section along plane III-III from Fig. 1

Fig. 1 shows a perspective depiction of the microtiter plate with vessels (3). The frame (1) has a length of a = 127 mm and a width of b = 85 mm. The lid (4) with projections (5) is shown in the lifted-off state.

Fig. 2 depicts a section along plane II-II. The glass base (2) is fastened underneath the microtiter plate. The edge distance (a1) is 3 - 8 mm, preferably 6 mm, and the distance (a2) is 6 - 11 mm, preferably 9.5 mm. The corresponding edge distance (b1) in Fig. 3 is likewise 3 - 8 mm, preferably 6 mm, and the distance (b2) is 4 - 11 mm, preferably 6.5 mm. The distances between the center of the outer vessels (wells) and the edge of the glass base (a3, b3) are 4 – 11 mm. The height of the frame of the microtiter plate is c = 6 – 20 mm, preferably 6 – 15 mm, particularly preferably 6 mm, and the inner height c1 is 3 - 12 mm, preferably 3 mm. The vessel diameter (d) is between 1.0 and 1.8 mm, particularly preferably

1.3 mm, the vessel distance (a4) is 2.25 mm and the vessel height (h) is between 2.0 and 7.0 mm.

Patent claims:

1. A miniaturized microtiter plate which has a body made of plastic and a base made of glass, and has 1000 to 4000 vessels (wells) (3), the diameter of the vessels (wells) (d) is 1.0 to 1.8 mm, the base of the microtiter plate (2) has a thickness of 0.07 - 0.2 mm, the distance between the center of the outer vessels (wells) and the edge of the glass base is 4 to 11 mm, and the microtiter plate has a lid (4) to prevent evaporation.

2. A miniaturized microtiter plate as claimed in claim 1, which has 1400 to 2500 vessels (wells), the diameter of the vessels is 1.2 to 1.5 mm, and the base of the microtiter plate has a thickness of 0.12 to 0.17 mm.

3. A miniaturized microtiter plate as claimed in claim 1 and/or 2, which has 1536 vessels (wells).

4. A miniaturized microtiter plate as claimed in claims 1 to 3, wherein the base of the microtiter plate has a thickness of 0.15 mm.

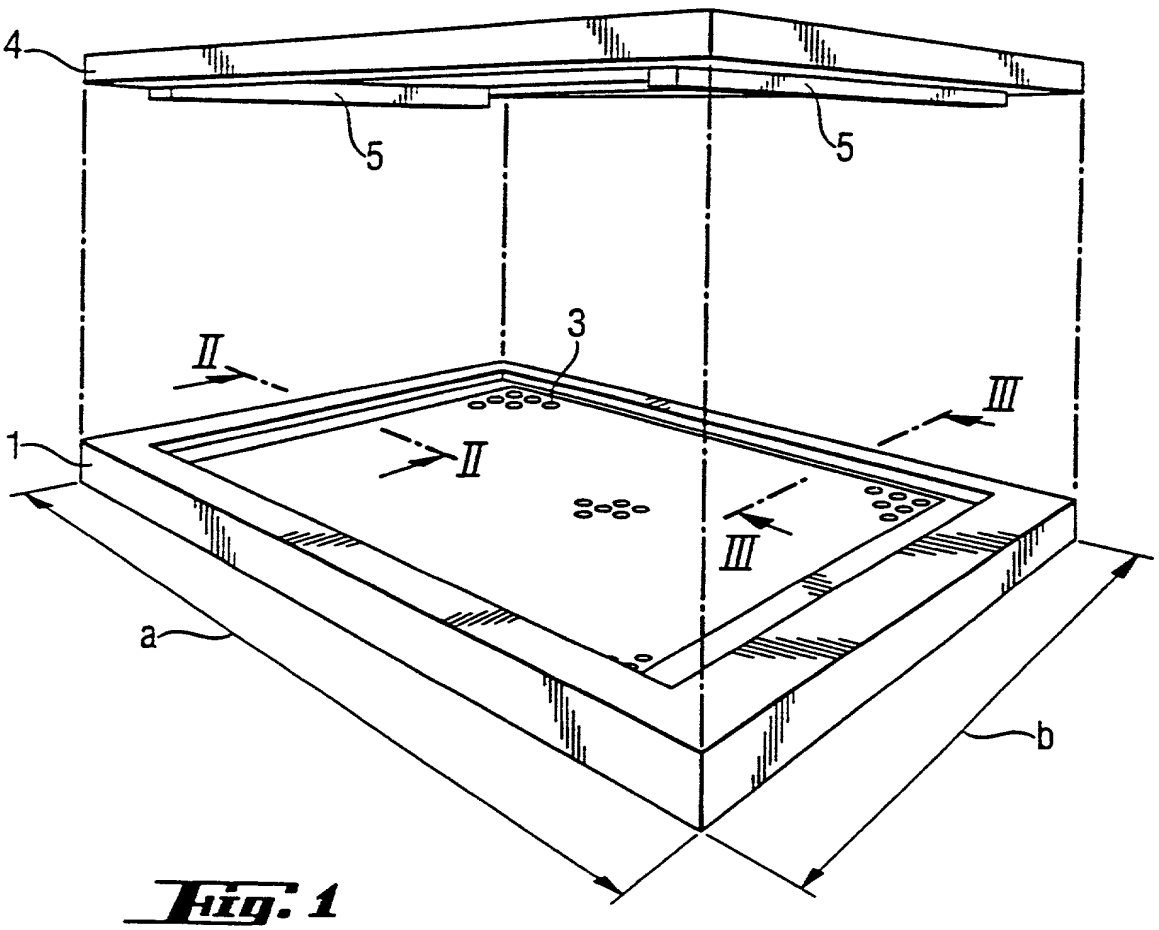


Fig. 1

Fig. 2

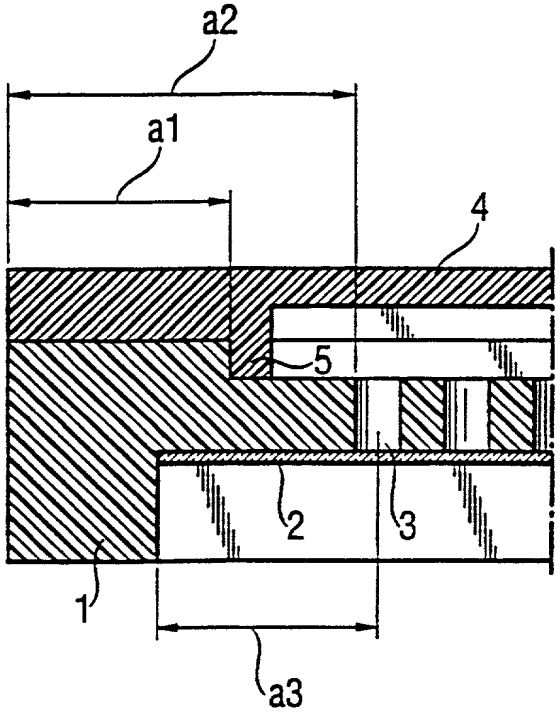
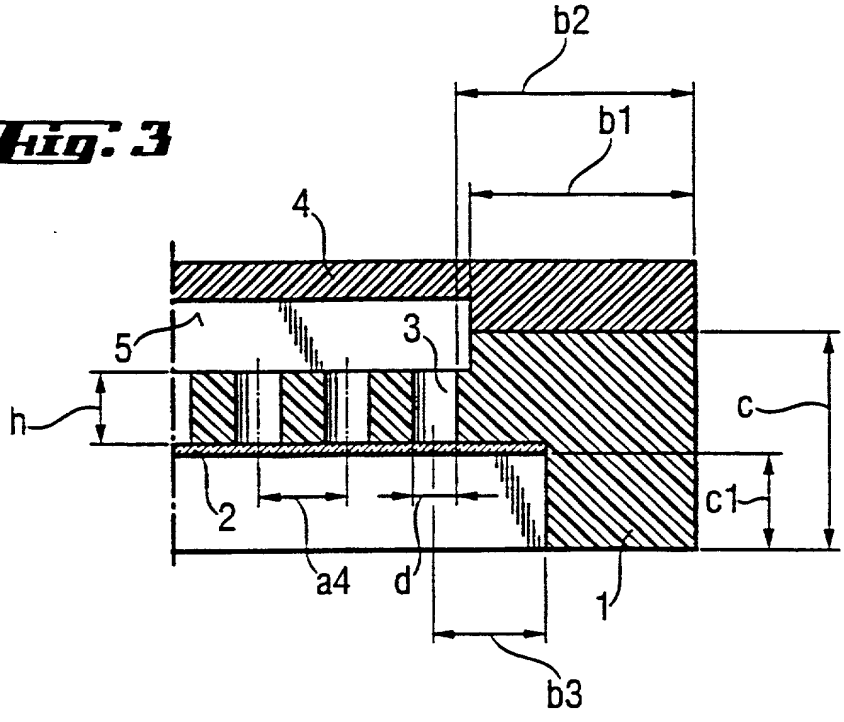


Fig. 3



COMBINED DECLARATION FOR PATENT APPLICATION AND POWER OF ATTORNEY

As below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below, I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

Miniaturized microtiter plate for HT-screening

the specification of which
was filed on March 17, 1999 as International Patent Application PCT/EP99/01729
I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims.

I acknowledge the duty to disclose to the Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, §1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Prior Foreign Application(s) for which Priority is Claimed:

Federal Republic of Germany, 29805613.5 of March 27, 1998
Federal Republic of Germany, 19836505.5 of August 12, 1998
Federal Republic of Germany, 29817256.6 of October 01, 1998

And I hereby appoint
Douglas B. Henderson, Reg.No. 20,291; Arthur S. Garrett, Reg.No. 20,338
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all of the firm of FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, Reg.No. 22,540, my attorneys, with full power of substitution and revocation to prosecute this application, to make alterations and amendments therein, to file continuation and divisional applications thereof, to receive the Patent, and to transact all business in the Patent and Trademark Office and in the Courts in connection therein, and specify that communications about the application are to be directed to the following correspondence address:

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

INVENTOR(S) / Residence

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Signature: H. Vollert Henning Vollert Date: 4.4.2000

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